CARDIOVASCULAR MEDICINE

Interaction between arrival time and thrombolytic treatment in determining early outcome of acute myocardial infarction

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Background: Shortening prehospital delay has been identified as an important means of improving responses to reperfusion treatment. If this increases the risk profile of the population delivered to hospital, it may paradoxically cause a deterioration in hospital mortality.
Objective: To examine the interaction between arrival time (time from onset of chest pain to arrival at hospital) and thrombolytic treatment in determining the early outcome of acute myocardial infarction.
Methods: Prospective cohort study of 1723 patients with acute myocardial infarction who were potentially eligible for thrombolytic treatment (ST elevation on ECG; arrival time ⩽ 12 hours).
Results: All patients were eligible for thrombolysis but only 1098 (80%) received it. Patients who did not receive thrombolytic treatment were older (66 (58–73) *v* 61 (53–70) years, p < 0.001), more commonly female (32.1% *v* 24.8%, p < 0.01), and had higher frequencies of previous infarction (28.6% *v* 15.6%, p < 0.001) and left ventricular failure (37.5% *v* 26.9%, p < 0.01) than patients who received thrombolytic treatment. For the group as a whole, 30 day mortality was 11.7% and was unaffected by arrival time, but in patients who did not receive thrombolysis an arrival time of ⩽ 6 hours was associated with significantly higher 30 day mortality than an arrival time of 6–12 hours (24.3% *v* 2.6%, p = 0.002). Conversely, in patients who did receive thrombolysis an arrival time of ⩽ 6 hours was associated with a lower 30 day mortality than an arrival time of 6–12 hours (8.5% *v* 14.5%, p < 0.02).
Conclusions: Shortening prehospital delay in acute myocardial infarction will tend to increase the risk profile of patients presenting to emergency departments. The data presented here indicate that this may increase hospital mortality if underutilisation of thrombolytic treatment among high risk groups is not diminished.

Randomised trials of thrombolytic treatment in acute myocardial infarction have consistently shown significant mortality reductions, particularly for patients with ST segment elevation treated within 12 hours of symptom onset.[1] The importance of early treatment has led to the development of strategies to reduce the time between symptom onset and arrival at hospital in order that more patients are delivered to emergency departments early after coronary occlusion when risk is greatest.[2] While this is desirable at the population level, reductions in arrival time must inevitably increase the risk profile of patients receiving hospital treatment, simply because a proportion of those very sick patients who would have died in the community will now reach hospital. It is not known what effect this might have on local mortality statistics.[3–5] This question is important because the 30 day mortality rate for acute myocardial infarction is a key criterion by which hospital performance is now assessed. In the present study, therefore, we have examined the influence of arrival time (time from the onset of symptoms to arrival at hospital) and its interaction with thrombolytic treatment in determining early mortality after acute myocardial infarction.

METHODS

Patient population

This was a single centre study (at Newham General Hospital) of 1725 patients with acute myocardial infarction, all of whom were potentially eligible for thrombolytic treatment (chest pain with ST segment elevation on ECG and ⩽ 12 hours between the onset of symptoms and arrival at the hospital emergency department). There are no facilities for primary coronary angioplasty at Newham. Data for thrombolytic treatment were available in 1723 patients who constitute the study group. The patients were logged onto the coronary care unit database during a 14 year period from 1988. Only patients with a first admission during that period were included.

Data collection

Baseline clinical characteristics including demographic, clinical, and biochemical data were collected prospectively and stored on a purpose built electronic database. The duration of pain before presentation at hospital was recorded, as was emergency treatment with thrombolytic drugs. Diabetes was recorded in patients on insulin, oral hypoglycaemic drugs, or dietary restriction. Hypertension was recorded in patients taking antihypertensive drugs. All admission drugs, including β blockers, were also recorded.

Statistical analysis

Comparison of discrete variables was by χ^2 analysis and continuous variables by the Mann–Whitney test. In order to evaluate their independent influence, baseline variables that were significantly different ($p < 0.05$) in univariate analysis or believed to be of clinical or biological relevance were entered into a logistic regression analysis. Odds ratios are quoted, together with 95% confidence intervals (CI). For survival comparisons at 30 days we used the log rank (Mantel–Cox) test.

Table 1 Baseline characteristics and complications in 1723 patients eligible for thrombolytic treatment, stratified by thrombolytic treatment and arrival time

	No thrombolysis (n=343)	Thrombolysis (n=1380)	Arrival ⩽6 h (n=1549)	Arrival >6 h (n=176)
Age (years)	66 (58 to 73)	61 (53 to 70)***	62 (53 to 71)	66 (58 to 72)**
Male sex	233 (67.9)	1038 (75.2)**	1149 (74.2)	124 (70.5)
Risk factors				
Hypertension	121 (35.8)	443 (32.4)	513 (33.4)	51 (29.7)
Diabetes	76 (22.4)	304 (22.1)	343 (22.2)	37 (21.1)
Current smoking	166 (49.7)	634 (46.5)	714 (46.8)	87 (50.3)
Emergency aspirin	221 (14.5)	1302 (85.5)***	1365 (91.0)	159 (93.5)
Infarct characteristics				
Anterior infarction	149 (44.2)	617 (45.8)	680 (44.9)	86 (49.7)
Q wave infarction	268 (78.8)	1080 (78.7)	1211 (78.7)	139 (79.4)
Previous infarction	98 (28.6)	215 (15.6)***	282 (18.3)	31 (17.8)
Peak CK (IU/l)	1012 (510 to 1892)	1169 (496 to 2038)	1162 (498 to 2030)	1022 (503 to 1812)
Complications				
VF	51 (15.0)	92 (6.7)***	137 (8.9)	6 (3.4)**
Heart failure	128 (37.5)	370 (26.9)**	437 (28.3)	62 (35.2)
Hospital death	67 (21.9)	106 (9.1)***	180 (11.6)	21 (11.9)

Data are n (%) for categorical variables and median (interquartile range) for continuous variables.
*p<0.05, **p<0.01, ***p<0.001.
CK, creatine kinase; VF, ventricular fibrillation.

RESULTS

Baseline characteristics stratified by thrombolytic treatment and arrival time

These data are given in table 1. Of the 1723 patients, all were eligible for thrombolytic treatment by ST segment and arrival time criteria, but only 1380 (80%) received it. Proportions of patients arriving at hospital within six hours of the onset of chest pain showed no significant differences year on year. However, these patients were younger and more likely to develop ventricular fibrillation than patients arriving later, although rates of thrombolysis (80.3% *v* 78.4%) and aspirin treatment (91.0% *v* 93.5%) were similar between the groups. Patients who received thrombolysis were more likely to receive adjuvant treatment with aspirin and were also younger and more commonly male.

Complications were less common among patients who received thrombolytic treatment, rates of heart failure and hospital death being 26.9% and 9.1%, respectively, compared with 37.5% and 21.9% in patients who did not receive treatment ($p < 0.001$). Reasons for not giving thrombolytic treatment were recorded in a subgroup of 142 patients recruited from 2000 onwards, of whom 25 (18%) were not treated. In three cases this was because of "haemorrhagic risk", in two because it was "too late" (notwithstanding hospital arrival within 12 hours), and in the remaining 20 (80% of untreated patients) because of "administrative failure".

Arrival time and hospital complications

These data are presented in table 2. All patients arrived within 12 hours of the onset of chest pain. For the group as a whole, hospital mortality was 11.7% and was unaffected by arrival time. However, in patients who did not receive thrombolysis, an arrival time of ⩽ 6 hours was associated with a more complicated hospital course, as reflected by higher rates of heart failure (38.6% *v* 28.9%, $p = 0.06$) and death (24.3% *v* 2.6%, $p = 0.002$), compared with an arrival time of 6–12 hours. Conversely, in patients who did receive thrombolysis an arrival time of ⩽ 6 hours was associated with a less complicated hospital course, as reflected by lower rates of heart failure (25.8% *v* 37.0%, $p = 0.005$) and death (8.5% *v* 14.5%, $p = 0.02$), compared with an arrival time of 6–12 hours. Of major complications, only ventricular fibrillation was unaffected by thrombolytic treatment, being more common for arrival times ⩽ 6 hours, regardless of treatment.

Arrival time and 30 day mortality

Data on arrival time and 30 day mortality are given in fig 1 and table 3. The 30 day mortality, available for the 1377 patients admitted between 1987 and 1997, was 13.4% and was unaffected by arrival time. However, Kaplan–Meier analysis confirmed that among patients who did not receive thrombolytic treatment, estimated survival at 30 days was significantly lower for an arrival time ⩽ 6 hours than for an arrival time of

Table 2 Complications of myocardial infarction according to thrombolytic treatment and stratified by arrival time in 1723 patients eligible for treatment

	Arrival time ⩽6 h (n=1549)	Arrival time >6 h (n=176)	p Value
No thrombolysis (n=343)			
VF	49 (16.2)	2 (5.3)	0.08
LVF	117 (38.6)	11 (28.9)	0.06
Hospital death	74 (24.3)	1 (2.6)	0.002
Thrombolysis (n=1380)			
VF	88 (7.1)	4 (2.9)	0.06
LVF	319 (25.8)	51 (37.0)	0.005
Death	106 (8.5)	20 (14.5)	0.02

Data are n (%).
LVF, left ventricular failure; VF, ventricular fibrillation.

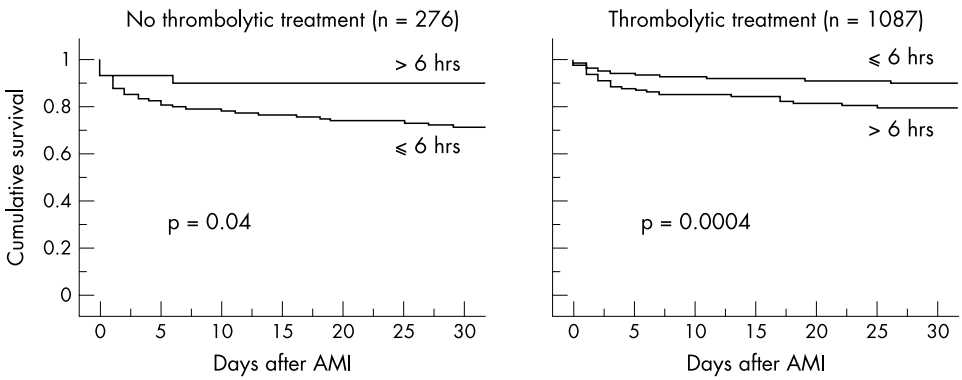

Figure 1 Kaplan–Meier curves in patients eligible for thrombolysis showing 30 day survival stratified for arrival time (⩽ 6 hours, and > 6 hours). Data for patients who did not receive thrombolysis are shown in the left panel and those for patients who did receive thrombolysis are shown in the right panel.

6–12 hours (72.4%, 95% CI 66.8% to 78.0% *v* 90.3%, 95% CI 79.9% to 100%; p = 0.04). Conversely, among patients who did receive thrombolytic treatment survival at 30 days was higher for an arrival time ⩽ 6 hours than for an arrival time of 6–12 hours (91.0%, 95% CI 89.0% to 93.0% *v* 79.3%, 95% CI 70.6% to 88.1%; p = 0.0004). Multivariate analysis confirmed that early arrival tended to increase the risk of death at 30 days if thrombolytic treatment was not given (odds ratio 2.12, 95% CI 0.55 to 8.11) but to reduce the risk if thrombolytic treatment was given (odds ratio 0.55, 95% CI 0.30 to 0.99).

DISCUSSION

In acute myocardial infarction, strategies to reduce the time between symptom onset and arrival at hospital will tend to increase the risk profile of patients presenting to emergency departments. Our data show that this may adversely affect local mortality statistics if a corresponding increase in the rate of thrombolytic treatment is not achieved.

This was a selected population of patients who fulfilled electrocardiographic and arrival time criteria for thrombolytic treatment. This allowed us to evaluate the benefits of treatment according to arrival time without distortion caused by patients who were not candidates for treatment based on late arrival or non-diagnostic ECGs, the usual reasons for ineligibility.[6] Although all our patients were potentially eligible for thrombolytic treatment, the treatment was underutilised and 20% of patients did not receive it. The data confirm our earlier observation[7] that those patients who did not receive thrombolysis fared less well—as reflected by a substantially higher rate of complications, including heart failure and hospital death—than patients who did receive treatment. Among patients who did not receive thrombolytic treatment, those who arrived at the emergency department within six hours of the onset of chest pain had a particularly high hospital mortality, and only 74.4% survived to 30 days. This contrasts with the more favourable outcome in those who arrived later, a self selected group of survivors, more than 90% of whom were still alive at 30 days despite receiving no thrombolytic treatment. Among patients who received thrombolytic treatment, the pattern was quite different, treatment within six hours being associated with a significantly lower 30 day mortality than later treatment. This accords with the data from clinical trials[2] and emphasises the importance of early reperfusion for reducing myocardial injury and complication rates.

The natural explanation for our findings is that non-administration of thrombolytic treatment itself accounts for the unfavourable outcome among patients presenting early, caused by failure of the myocardial protection that would have occurred with successful reperfusion. The low rate of aspirin treatment in the same patients who were denied thrombolysis no doubt played a complementary role, aspirin reducing the odds of 30 day mortality regardless of whether thrombolytic treatment was given or not. However, the multivariate contribution of early arrival to 30 day mortality was weak, and other explanations for the unfavourable outcome in those who did not receive thrombolytic treatment merit consideration, particularly the possibility that treatment was prejudicially withheld in higher risk patients and those with more extensive myocardial injury. Certainly, reasons for non-administration of thrombolysis in our small subgroup analysis were not usually clinically driven but resulted instead from "administration failure"—a term used in the national audit process to indicate that "thrombolytic treatment was withheld incorrectly."[8] For example, as we and others have previously reported,[9–11] elderly patients were less likely to receive thrombolytic treatment, although this is unlikely to provide a full explanation for our observations as they were also more likely to arrive late, when outcome improved for untreated patients. Whether complications, particularly left ventricular failure, deterred emergency staff from giving thrombolytic treatment cannot be deduced from our data, but it is noteworthy that left ventricular failure was significantly more common among untreated patients and was the major determinant of outcome regardless of thrombolysis. Women and patients with a history of previous myocardial infarction were also over-represented among those who did not receive thrombolytic treatment, and

Table 3 Multivariate baseline predictors of 30 day mortality according to thrombolytic treatment

	No thrombolysis	Thrombolysis
	(274 complete datasets analysed)	(1079 complete datasets analysed)
Arrival time ⩽6 h	2.12 (0.55 to 8.11)	0.55 (0.30 to 0.99)*
Age	1.04 (1.00 to 1.07)*	1.06 (1.03 to 1.08)***
LVF	4.72 (2.41 to 9.24)***	6.56 (4.11 to 10.49)***
Male sex	0.47 (0.24 to 0.92)*	0.87 (0.53 to 1.42)
Q wave MI	1.79 (0.59 to 5.49)	3.31 (1.46 to 7.50)**
Emergency aspirin	0.25 (0.13 to 0.49)***	0.28 (0.14 to 0.60)***

Data are odds ratios (95% confidence interval).
*p<0.05, **p<0.01, ***p<0.001.
LVF, left ventricular failure; MI, myocardial infarction.

while this is not a new observation,[11] it emphasises the potential for improving outcome in acute myocardial infarction by targeting these high risk groups.

The 20% of patients who did not receive thrombolysis were all potentially eligible for treatment based on ST segment elevation and arrival within 12 hours of the onset of chest pain. Our subset analysis confirmed clinical contraindications to treatment in a small proportion of cases, such that the actual rate of "underutilisation" in the present study was almost certainly less than 20%. This is substantially lower than the 30–33% underutilisation rates recently reported by the GRACE (global registry of acute coronary events) and TRACE (trandolapril cardiac evaluation) investigators among patients with acute myocardial infarction who fulfilled standard criteria for thrombolytic treatment.[11 12] Other investigators have also reported underutilisation rates of thrombolytic treatment that are substantially higher than those identified in our study.[13–15] Thus the impact on hospital mortality of increasing the numbers of patients presenting early to emergency departments in response to strategies for rapid referral could be substantial, depending largely on local underutilisation rates of thrombolytic treatment. We found that non-administration of thrombolytic treatment in patients presenting early was associated with a very high mortality, and if mortality statistics are not to deteriorate underutilisation must be minimised. Indeed, the TRACE investigators found that "overutilisation" of thrombolytic treatment among patients not fulfilling standard indications was associated with reduced mortality and concluded that treatment should be evaluated in wider patient categories, particularly those with a bleeding risk based on events some time in the past.[12]

Conclusions

Strategies to reduce arrival times are likely to increase the proportion of high risk patients delivered to emergency departments. Our data indicate that this may increase hospital mortality if underutilisation of thrombolytic treatment is not reduced, particularly among elderly patients, women, and other high risk groups. Maximising the rate of treatment within existing criteria should be the primary objective,[16] together with greater application of primary angioplasty where appropriate.[17] Nevertheless, on the basis of evidence from other investigators,[12] there may also be a need to extend indications for thrombolysis to patients in whom it would normally be considered inappropriate. Prolonged cardiopulmonary resuscitation, for example, is normally regarded as a contraindication to thrombolysis but a recent study has effectively refuted this.[18] There has now been a call for further trials to examine the scope for extending the range of indications for thrombolytic treatment in acute myocardial infarction.[19]

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